Synopsis

Abbott Laboratories	**Individual Study Table Referring to Part of Dossier:**	**(For National Authority Use Only)**
Name of Study Drug: Adalimumab	**Volume:**	
Name of Active Ingredient: Adalimumab	**Page:**	

Title of Study:

A Multi-Center, Open-Label Study of the Fully Human Anti-TNF Monoclonal Antibody Adalimumab for the Induction and Maintenance of Clinical Remission in Subjects with Moderate to Severe Crohn's Disease

Coordinating Investigator:

Robert Lofberg, MD

Study Sites:

187 sites throughout Europe

Publications: 14

Studied Period (Years): First Subject First Visit: 04 December 2006 Last Subject Last Visit: 28 July 2008	**Phase of Development:** 3b

Objectives:

To further evaluate and delineate the safety and efficacy profile of adalimumab when administered to subjects with moderate to severe Crohn's disease (CD).

Efficacy:

- To evaluate the efficacy of adalimumab in the induction and maintenance of fistula closure.
- To evaluate the impact of adalimumab on extra-intestinal disease manifestations (EIMs).
- To measure clinical remission and response utilizing the Harvey-Bradshaw Index (HBI).
- To measure changes in patient reported outcomes (PRO) from Baseline.

Methodology:

This study consisted of a Screening period, treatment period, and follow-up period. Subjects were seen at Screening, Baseline, and Weeks 2, 4, 8, 12, 20, and every 12 weeks until marketing authorization of adalimumab. A follow-up telephone call was made to Subjects 70 days after they received the last dose of study medication.

At Baseline (Week 0), all subjects were to receive a subcutaneous (SC) loading dose of 160 mg adalimumab followed by 80 mg adalimumab SC at Week 2. Starting at Week 4, all subjects were to receive injections of adalimumab 40 mg every other week (eow) SC, except in the case of disease flare or non-response. Starting at Week 12, subjects who experienced a disease flare (defined as an increase in the HBI ≥ 3 and an HBI total score ≥ 7 compared with Week 4), or who were not responding to adalimumab (non-response was defined as a decrease in the HBI < 3 compared with Baseline) were permitted to increase to adalimumab 40 mg weekly (ew).

Subjects could switch (dose-escalate) to ew therapy after the Week 12 visit; the switch was to occur at an unscheduled visit between Week 12 and Week 18. For subjects who completed the study on eow therapy, the last dose of adalimumab was at Week 18. For subjects who completed the study on ew therapy, the last dose of adalimumab was at Week 19. For subjects who continued on study therapy past Week 20, dose escalation was allowed at or after Week 20.

Subjects were evaluated for safety and efficacy at Baseline (Week 0), Weeks 2, 4, 8, 12, and 20, and at unscheduled visits. Efficacy evaluations included HBI, Short Inflammatory Bowel Disease Questionnaire (SIBDQ), Work Productivity Activity Index (WPAI) questionnaire, fistula counts, health care resource utilization (HCRU), and evaluation of CD-related EIMs. Safety assessments included vital signs, physical examination, general laboratory analyses, urinalysis, and monitoring of adverse events (AEs).

Number of Subjects (Planned and Analyzed):

Planned: 1000 subjects

Enrolled: 945 subjects

ITT population: 945 subjects

Diagnosis and Main Criteria for Inclusion:

Men and women, between the ages of 18 and 75 years (inclusive), with moderate to severe CD of at least 16 weeks duration that did not adequately respond to conventional therapy; an HBI score of at least 7; adequate cardiac, renal, and hepatic function; and the ability to self-inject (or have a designee who could inject) study medication.

Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:

Adalimumab 40 mg/0.8 mL in 1-mL pre-filled syringe for SC injection

Baseline: 160 mg adalimumab

Week 2: 80 mg adalimumab

Week 4: 40 mg adalimumab administered eow

Week 12 or later:

Responder: 40 mg adalimumab eow

Non-responder or disease flare: 40 mg adalimumab administered ew

Lots:

Pre-filled Pen, Adalimumab, 40 mg/0.8 mL

Bulk Lot Number	Kit Range
06-006532	[redacted]
07-011387	[redacted]
06-006938	[redacted]
07-011930	[redacted]

Prefilled Syringe, Adalimumab, 40 mg/0.8 mL

Bulk Lot Number	Kit Range
06-006532	[redacted]

Duration of Treatment:

Up to 20 weeks, with extension possible.

Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number:

Not applicable.

Redacted information - 08Jun2012

Criteria for Evaluation

Efficacy:

- Proportion of subject in clinical remission (HBI total score < 5)
- Proportion of subjects with a response (decrease in HBI ≥ 3)
- Proportion of subjects with absence of draining fistulas at the last 2 evaluations
- Proportion of subjects with a reduction of at least 50% in the number of draining fistulas at the last 2 evaluations
- Mean number of days fistulas were draining (according to Investigator assessment)
- Proportion of subjects who developed new draining fistulas
- Mean number of draining fistulas per month
- HBI total score
- SIBDQ
- WPAI
- Proportion of subjects with development of CD-related EIMs
- Proportion of subjects with resolution of CD-related EIMs
- Proportion of subjects with unscheduled outpatient visits
- Proportion of subjects with emergency room (ER) visits
- Proportion of subjects with hospitalizations
- Crohn's Disease Activity Index (CDAI) conducted at 65 sites

Safety:

- AEs (serious and non-serious)
- Laboratory parameters
- Physical examination results
- Vital sign measurements

Statistical Methods

Both the efficacy and safety analyses were performed on the set of subjects who received at least one SC injection of adalimumab.

Efficacy:

Demographic and Baseline variables were described by summary statistics. For continuous data, n, mean, standard deviation (SD), minimum, 1st quartile, median, 3rd quartile, and maximum were presented. For categorical data, absolute and relative frequency was given.

Efficacy endpoints were assessed at Weeks 2, 4, 8, 12, and 20 and/or for changes in comparison with Baseline at Weeks 2, 4, 8, 12, and 20. Analysis was done descriptively by presenting summary statistics. Values at all visits, as well as changes from Baseline in HBI total score, SIBDQ, and WPAI were summarized.

For the mean change in total HBI score, SIBDQ, and WPAI, 95% confidence intervals (instead of a linear regression with the Baseline value as covariate) were calculated. The 95% confidence intervals for changes in work time missed (WPAI) and absolute values in HBI, SIBDQ, WPAI, mean days fistulas were draining, and the number of draining fistulas were not calculated because values were not normally distributed.

Only injections with total volume injected were included in the analyses.

Subgroup analysis was done descriptively by presenting summary statistics, and by the use of analysis of variance or logistic regression models, as appropriate.

Analysis of variance (ANOVA) and logistic regression models used for exploratory analysis did not include age and race as covariates, because the numbers in specific categories were too small. ANOVA models were not calculated for changes in work time missed (WPAI) and cumulative numbers from the HCRU questionnaire because values were not normally distributed.

In a subpopulation, HBI total score and CD Activity Index (CDAI) score were analyzed descriptively by presenting summary statistics for each visit, with correlation analysis of HBI total score and CDAI score calculated using Spearman's rank correlation coefficient for each visit.

Safety:

Treatment-emergent AEs (TEAEs) were summarized and were tabulated by MedDRA system organ class (SOC) and preferred term (PT). The number and percentage of subjects experiencing TEAEs were presented, as well as summaries of severity and relationship to study drug. TEAEs leading to premature withdrawal and other events of special interest were listed and described in detail.

Other safety variables, such as laboratory data, were described as mentioned above. In addition, shift tables and listings were provided for abnormal laboratory values, whereby the normal range of the analyzing laboratory was used.

Summary/Conclusions

Efficacy Results:

Positive results for remission and response (HBI), SIBDQ, WPAI scores, HCRU, changes in draining fistulas, and changes in CD-related EIMs showed that adalimumab was effective in the treatment of the study population with moderate to severe CD.

Analysis of the results for HBI showed clinically significant improvement in the combined score of general well being, abdominal pain, diarrhea, abdominal mass, and complications in subjects treated with adalimumab in both the observed data and LOCF analyses.

		N	Mean Change ± SD	Mean % Change ± SD
Observed	Week 12	857	–5.7 ± 4.45	–53.2 ± 38.37
	Week 20	798	–6.2 ± 4.26	–58.3 ± 34.70
LOCF	Week 12	941	–5.4 ± 4.64	–50.3 ± 40.28
	Week 20	941	–5.6 ± 4.67	–52.5 ± 39.86

Proportion of subjects in clinical remission (HBI total score < 5) and proportion of responders (decrease from Baseline ≥ 3 in the HBI total score) at Weeks 12 and 20:

		Proportion of Subjects in Clinical Remission (HBI Total Score < 5)	Proportion of Subjects who were Responders (Decrease from Baseline ≥ 3 in HBI Total Score)
		n/N (%)	
Observed	Week 12	457/857 (53.3)	688/857 (80.3)
	Week 20	492/798 (61.7)	658/798 (82.5)
NRI	Week 12	457/945 (48.4)	688/945 (72.8)
	Week 20	492/945 (52.1)	658/945 (69.6)

In order to compare the results of the HBI total score and the CDAI score, a corresponding CDAI score was calculated for all subjects who consented at approximately 65 sites. CDAI score showed a moderate to strong correlation with HBI results.

Results for the 4 domains of the SIBDQ (obtained from all subjects except those enrolled in Slovakia) were similar and indicated improved quality of life. The mean changes were greater than the minimally clinically important difference (MCID) of 9 points.

		N	Mean Change ± SD	Mean % Change ± SD
Observed	Week 12	816	13.6 ± 12.34	44.6 ± 49.57
	Week 20	763	14.7 ± 12.85	48.5 ± 52.77
LOCF	Week 12	907	12.9 ± 12.72	42.7 ± 50.19
	Week 20	907	13.2 ± 13.39	44.3 ± 53.09

Results for WPAI showed that a significant proportion of the subjects were unemployed throughout the study. With adalimumab treatment, subjects overall showed improvements in percent work time missed due to CD (absenteeism), percent overall work impairment, and percent activity impairment, starting from Week 2, and continued to improve through Week 20. The magnitude of improvement ranged from 1 to 3 times the MCID for all measures at Weeks 12 and 20.

		N	Mean Change ± SD	N	Mean % Change ± SD
Absenteeism					
Observed	Week 12	342	–10.1 ± 32.02	173	–41.7 ± 137.43
	Week 20	328	–9.8 ± 31.69	157	–42.2 ± 152.49
LOCF	Week 12	392	–10.1 ± 31.13	198	–43.9 ± 130.65
	Week 20	369	–10.8 ± 33.47	184	–43.1 ± 147.08
Presenteeism					
Observed	Week 12	381	–18.6 ± 29.95	358	–35.0 ± 69.67
	Week 20	360	–20.0 ± 30.91	337	–35.0 ± 88.66
LOCF	Week 12	402	–17.9 ± 29.56	377	–33.8 ± 69.02
	Week 20	382	–20.0 ± 30.89	359	–34.8 ± 86.43
Work Impairment					
Observed	Week 12	314	–21.1 ± 32.30	297	–37.0 ± 69.01
	Week 20	302	–21.4 ± 33.58	282	–32.3 ± 89.46
LOCF	Week 12	366	–19.9 ± 31.53	344	–34.3 ± 70.33
	Week 20	346	–21.8 ± 34.29	325	–31.7 ± 88.84
Activity Impairment					
Observed	Week 12	799	–24.4 ± 29.38	773	–38.9 ± 64.45
	Week 20	747	–25.9 ± 29.66	722	–41.0 ± 72.64
LOCF	Week 12	901	–23.0 ± 29.86	875	35.8 ± 65.46
	Week 20	902	–23.6 ± 30.58	876	–36.2 ± 73.42

In the analysis of observed HCRU data, the number and percentage of subjects requiring health care resources since the last visit tended to increase from Week 2 through Week 20. This is probably related to the increased length of the interval between scheduled visits after Week 4 and Week 12. Specific measures of HCRU were the mean number of unscheduled outpatient visits, ER visits, hospitalizations, and days in hospital, all of which were low throughout the study.

The mean number of draining fistulas and the proportion of subjects with development of new draining fistulas were low throughout the study using observed and LOCF data. The proportion of subjects with absence of fistulas and a ≥ 50% reduction in the number of draining fistulas are presented below.

		Mean Number of Draining Fistulas	
		N	**Mean ± SD**
Observed	Week 12	858	0.2 ± 0.91
	Week 20	802	0.2 ± 0.91
LOCF	Week 12	942	0.2 ± 0.89
	Week 20	942	0.2 ± 0.89

		Number (%) of Subjects with Development of New Draining Fistulas	**Number and Percentage of Subjects with Absence of Draining Fistulas**	**Number and Percentage of Subjects with a ≥ 50% Reduction in the Number of Draining Fistulas**
Observed	Week 12	8/858 (0.9)	44/158 (27.8)	51/158 (32.3)
	Week 20	11802 (1.4)	45/148 (30.4)	53/148 (35.8)

While the incidence of CD-related EIMs appeared to increase during the study, the increase is explained by the fact that the number of subjects with a CD-related EIM are cumulative at each visit. The rate leveled off over time, which seems to reflect the positive effect of adalimumab.

		Number and Percentage of Subjects with Development of CD-related EIMs	**Number and Percentage of Subjects with Resolution CD-related EIMs**
Observed	Week 12	191/858 (22.3)	342/442 (77.4)
	Week 20	215/803 (26.8)	346/417 (83.0)
NRI	Week 12	278/945 (29.4)	342/497 (68.8)
	Week 20	357/945 (37.8)	346/497 (69.6)

Overall, efficacy results showed the greatest improvements in subjects who continued to receive adalimumab 40 mg eow throughout the study. Subjects who required escalation to ew dosing because of CD flare or loss of response also showed steady improvement, albeit less pronounced when compared with those who did not require dose escalation. This reflected the more severe disease experienced by subjects who underwent dose escalation.

Subgroup analyses of efficacy results tended to show strong relationships between poorer response to adalimumab treatment and prior infliximab use, and better response to adalimumab treatment and concomitant use of immunosuppressants at Baseline, and Baseline CRP ≥ 1.0 mg/dL.

In qualitative and quantitative efficacy measures, subjects with prior infliximab failure showed lesser improvements in HBI scores and certain other efficacy scores than the overall population of adalimumab-treated subjects in this study. However, the subjects with prior infliximab failure showed clinically meaningful improvements in most measures.

Safety Results:

In this study, adalimumab was found to be safe and well-tolerated in subjects with moderate to severe CD.

No deaths occurred during the study.

Most subjects had at least one TEAE during the study (79.8%). The highest incidences of TEAEs were for headache and nasopharyngitis. All other TEAEs occurred in ≤ 5% of all subjects. Most subjects had TEAEs that were mild to moderate in severity. Approximately half (47.3%) the subjects had at least one TEAE that was at least possibly drug related.

A total of 181 subjects (19.2%) had SAEs, the most frequently occurring being CD (worsening of) (5.7%). All other individual SAEs occurred in ≤ 1% of subjects.

One hundred subjects (10.6%) had TEAEs that led to discontinuation. Most were gastrointestinal in nature.

The incidence of TEAEs of special interest was low with the exception of infections and injection site reactions. Infections occurred in 45.7% of subjects, the most frequent being nasopharyngitis (14.4%) and bronchitis (4.3%). All other infections occurred in ≤ 4% of subjects. Serious infections occurred in 5.3% of subjects, but all single events occurred in ≤ 1% of subjects. Six subjects had opportunistic infections that were considered possibly or probably related to study drug, but all single events occurred in ≤ 1% of subjects. All but one of the subjects was female, and all of the infections involved candidiasis. All but one of the opportunistic infections resolved during the study. No cases of disseminated candidiasis were reported. Injection site reactions occurred in 113 subjects (12.0%), the most frequently occurring being injection site pain, injection site erythema, and injection site pruritis. All other injection site reactions occurred in ≤ 2% of subjects.

All other TEAEs of special interest were reported by ≤ 5% of subjects. There were no reports of serious allergic reactions, lymphoma, congestive heart failure, lupus or lupus-like reactions, or tuberculosis.

Assessments of clinical laboratory test results (hematology, clinical chemistry, and urinalysis) and vital signs showed no clinically relevant findings.

Thirteen subjects became pregnant during this study. Two of them chose to have an elective abortion and one subject had a spontaneous abortion. All three were reported as SAEs.

There were 11 live births (including a set of twins). Three of the births including the set of twins were premature (36, 35 and 35 weeks gestation). Babies born before the 37th week of pregnancy were considered premature. One subject delivered at 42 weeks.

There were no medically significant complications and no birth defects reported.

Conclusions:

Efficacy results of this study showed the efficacy of adalimumab in inducing clinical remission and response utilizing the HBI, inducing and maintaining fistula closure, reducing CD-related EIMs, and improving PROs from Baseline. Clinically meaningful improvements were seen even in subjects who required escalation to ew dosing.

Safety data from this study confirm that adalimumab is generally well tolerated in subjects with moderate to severely active CD. The safety findings raise no new or unexpected issues related to the use of adalimumab in the treatment of CD.

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